

nivolumab and denosumab. She completed 10 cycles till April 2017 when she had disease progression. A lesion was found on the liver and the lung nodules increased in size and number. The therapy was changed to pazopanib while she remained on denosumab. She continued till May 2018, when she presented with disease progression in bones. A new therapy with cabozatinib and denosumab was initiated. Throughout these years, the patient was fully active as a physician for the UN.

In January 2019, a 7 mm mass was found in the right nephrectomy bed. The patient continued with her previous therapy until July 2019, when she noticed a mass in the oral cavity on the left side in the buccal mucosa of the retromolar trigone. After a consultation with her dentist, she started antibiotic therapy and stopped the targeted therapy. Due to persistent pain and numbness in the region of the mandible and speech difficulties, the patient visited a maxillofacial surgeon.

On physical examination, a soft mass with a smooth surface was seen in the oral cavity involving the left side buccal mucosa, measuring 2.7 x 0.8 x 0.9 cm. Blood and serum biochemistry examinations were within normal limits. The possibility of a medication related osteonecrosis of the jaw, attributed to the use of antiangiogenics with bone remodelling agents, was entertained, but one would have expected exposed bone, that was not present in this case.

Instead, the lesions were irregular growths. Gingival hypertrophy and an ingrown 3rd molar were considered. Due to the recent use of agents known to cause osteonecrosis of the jaw, invasive techniques were initially deferred, but once the diagnosis was suspected, a biopsy was scheduled. An excisional biopsy of the lesion located on the left side of the oral mucosa was performed (**Figure 1**) which was positive for metastasis from clear cell RCC (**Figures 2-7**).



Figure 1. Metastatic lesion on the left side during excision biopsy.

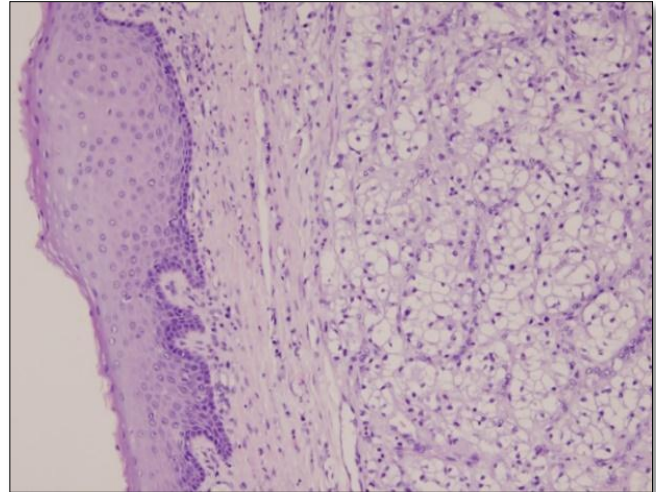


Figure 2. Buccal mucosa with infiltration of the lamina propria by a clear cell.

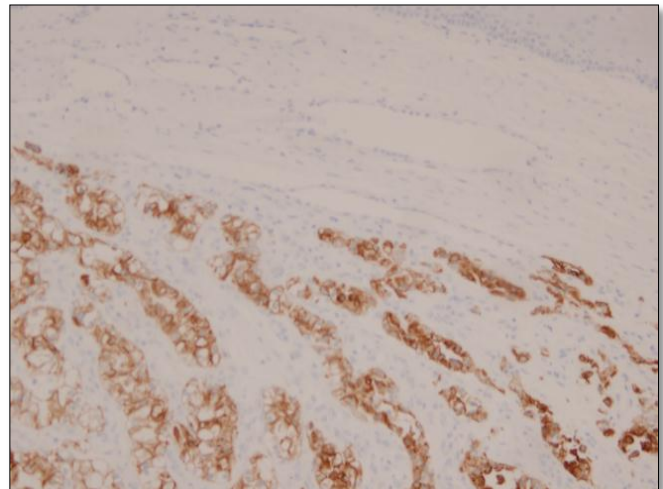


Figure 3. CK8 Epithelioid Neoplasm.

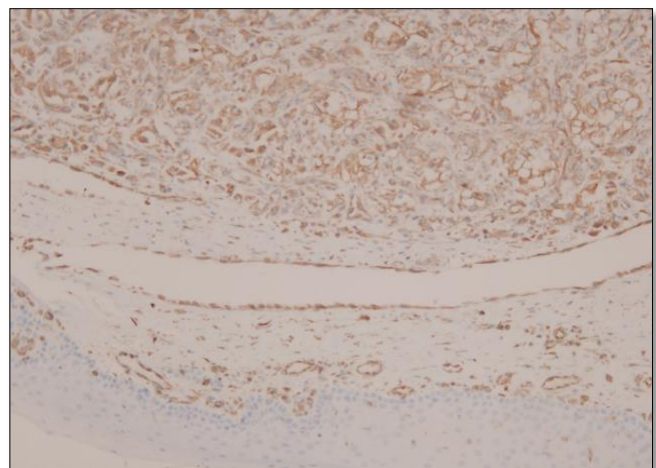


Figure 4. Vimentin.

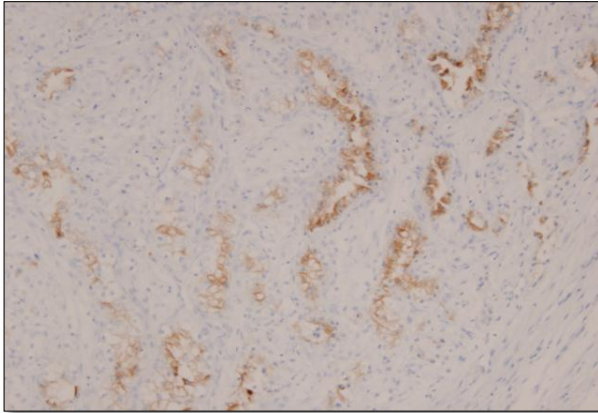


Figure 5. RCC.

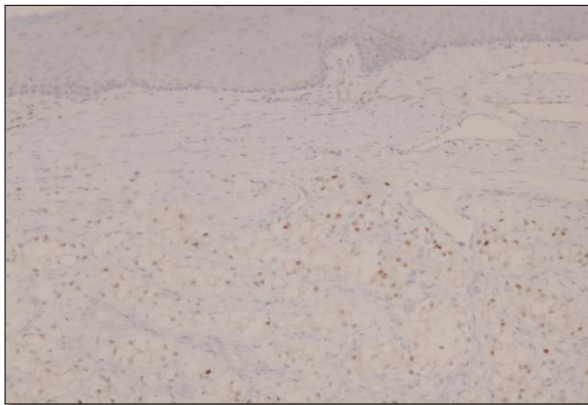


Figure 6. Pax-8.

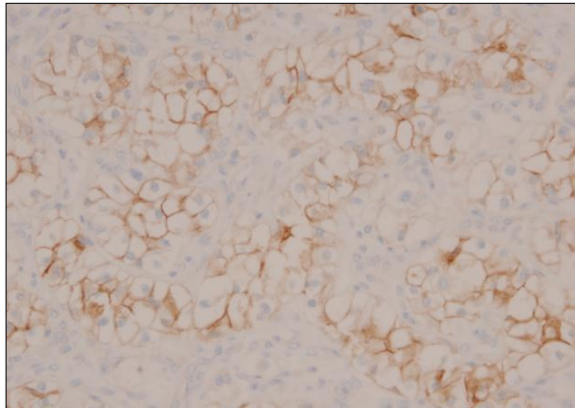


Figure 7. CD10.

Because she had persistent symptoms of right hip pain and mobility difficulties, she underwent a spinal and brain MRI with findings suspicious for meningeal spread of the disease, but CSF cytology was negative although CSF protein was elevated at 55.6 mg/dL. Furthermore, the abdominal MRI revealed lesions in the area of the right adrenal gland, on the left adrenal gland, in the paraspinal soft tissues and in the pulmonary bases bilaterally. The patient was started on

axitinib in July 2019. In the first weeks of therapy, a new lesion appeared on the right side of the oral cavity but by September 2019, complete remission of the mass on the left side was reported (Figure 8) and significant reduction in the size of the one located on the right side (Figure 9). Furthermore, the jaw numbness subsided. Her latest MRI in November 2019 showed significant reduction of the lesions on the adrenal gland and the soft tissues, while, milder radioisotope enhancement was evident in the metastatic bone lesions in a bone scan. The patient is in a good clinical condition and since December 2019, the lesion on the right side of the oral cavity is also in complete remission. In January 2020 pembrolizumab was added to the therapeutic regimen due to a new disease progression in bones and lung.



Figure 8. Shrinkage of the lesion on left side.



Figure 9. Lesion on right side.

DISCUSSION

Oral metastases are uncommon and can occur either to the oral soft tissues or to the jaw bones. The literature suggests that there is a strong association between oral metastases and the presence of teeth (as an important determinant on oral site preference for metastases) and inflammation. Actually, chronically inflamed gingivae can be a favorable environment for tumor cells to colonize and proliferate [1].

Because of its rarity and the lack of extensive literature, gingival metastatic disease usually presents as case reports and case series. The diagnosis of a metastatic lesion in the oral region is challenging, both to the clinician and to the pathologist. Early diagnosis and histological confirmation may lead to the appropriate treatment [8].

The treatment of oral metastases may include surgery, chemotherapy, immunotherapy, radiotherapy and targeted therapy. Choice of treatment is based upon the stage of the disease, the primary location of the tumor and patient related factors such as age. Oral metastases usually occur in the advanced stages of cancers, and the prognosis is usually poor [9]. Due to this, cancer patients with oral lesions deserve careful diagnostic evaluation. Biopsy is always necessary in order to make a definite diagnosis and start the appropriate treatment. Doctors whose role is critical in the prompt identification and management of oral metastases are dentists, ENT and maxillofacial surgeons because they might be the first ones to detect the lesions located in the oral cavity.

Furthermore, in the era of bone remodelling agents and antiangiogenic agents the concern that a biopsy may lead to medication related osteonecrosis of the jaw can lead to misdiagnosis and may hinder physicians from acting promptly.

Another accompanying symptom encountered on this patient was numbness of the jaw. This is a much more frequent symptom usually called frozen chin and associated with leptomenigeal disease or bone metastases in the jaw, described in the literature also as mental nerve neuropathy. Benign or malignant neoplasms can affect the function of the mental nerve causing this symptom. Patients sometimes do not report paresthesia but careful intra oral and extra oral examination reveal altered sensation in the lips and chin [10].

In this patient, the symptom subsided with overall response to therapy and it is unclear whether it was directly associated with the gingival metastases but at the time a spinal tap was performed and the CSF cytology was negative, although imaging was suggestive of leptomenigeal metastases. Interestingly the jaw numbness recurred despite the remission of the oral metastases.

According to an analysis of 673 cases which was published in 2007, [4] it appears that the median onset time of oral

metastases after the discovery of the primary tumor is about 40 months. By reviewing the previously reported cases of soft tissue metastases in patients with RCC, it appears that the median onset time is 18 months, although in one third of the cases the metastases can be found before the primary tumor [11]. Most patients presenting with oral metastases are male and the average age at presentation of oral lesions is 60 years. In the majority of the cases, the patients presented with painless local swelling. Two patients presented with severe gingival pain and one with gingivorrhagia and difficulty chewing and swallowing. In the case reports where the oral lesion was found before the primary kidney tumor, the provisional diagnosis of pyogenic granuloma was made [12-20]. In this case report, the gingival lesion appeared 35 months after the initial diagnosis, which is longer than average, the patient was female and her age when the lesion appeared was 65 years old.

Clinical cases that involve metastases to the oral cavity mucosa should be reported due to their rarity in order to alert physicians to their existence.

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